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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/661,172	09/13/2003	Jason C. H. Shih	5051-653	7508

20792 7590 06/19/2006

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EXAMINER	
WALICKA, MALGORZATA A	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 06/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/661,172	SHIH ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03/13/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The Amendment filed March 31, 2006 is acknowledged. Claim 4 has been currently canceled. Claims 14-30 have been previously canceled. Claims 1, 2, 3, 5, 6, 7, 9, 10-13 have been amended. Claims 1-3 and 5-13 are pending and under examination.

DETAILED ACTION

1. Objections

The objection for lack of compliance of nucleotide sequence disclosure with 37 C.F.R 1.821-1.825 made in the Office action of Dec. 29, 2005 (previous action) is withdrawn, because Applicants filed computer and paper sequence listing as well as the statement of their sameness.

The specification was objected to for lack of catalog number and the full address of the DSM firm of Holland, wherefrom the pLAT8 plasmid was purchased. This objection is withdrawn, because the specification contain the relevant information.

The specification is objected to because the chapter **"Gene Cloning, Transformation and Integration in *B. Licheniformis* DB104"** on page 5 refers to *B. subtilis* DB104, transformed with vectors listed in Table 2. Furthermore, on page 9, third line from the bottom, Applicants suggest that B. subtilis was transformed to contain the plasmid extrachromosomally and not integrated;

> "Compared the *B. subtilis* expression system, stable integrants producing higher enzyme activity were developed. Unlike the plasmid–containing expression system in *B. subtilis*, the chromosomal integration of *kerA* in *B.*

licheniformis avoided the segregational and structural instability common to replicative plasmids".

Please clarify typographical errors and ambiguity of the subject.

Claims

Objection to claim 1 made in the previous action is withdrawn, because the claim has been amended.

Clam 1 is objected to because one skilled in the art does not "collect" an enzyme from the medium but isolates it therefrom.

2. Rejections

2.1. 35 U.S.C. 112, second paragraph

Claims 1-13 were rejected in the previous action. Rejection of claims 4 is moot because the claim has been cancelled. Rejection of claim 5-10 and 12-13 is withdrawn because the claims have been amended.

Claim 2 is confusing in recitation of the word "substrate" as it is unclear what substrate the Applicants mean. Do Applicants mean the nutrient in the medium or a keratinase substrate or other substrate? In their Remarks of March 31, 2006, page 5 of 10, Applicants respectfully submit that one skilled in the art would understand that 'substrate' as recited in Claim 2 refers to a protein source upon which an enzyme may interact." This explanation is not persuasive. Firstly, it is unknown which enzyme. Secondly, an enzyme does not interact on any source, but on the protein. Thirdly, is that a substrate for keratinase or for other enzyme?

Rejection of claim 3 for recitation the term "feather meal" is withdrawn, because Applicants provided description of feather meal. However, the internet printout describing the term "soy" is unsatisfactory. Certainly the producer' leaflet describes the content of that what is used in medium preparation and what in laboratory jargon is referred to as "soy". This is not a semantic dispute, because the "soy" influences expression of keratinase. Thus, a qualitative and quantitative description is proper.

Rejection of claim 11 is still unclear as "said recombinant Bacillus" clearly refers to the bacteria after transformation yet claim 11 is referring to limitations of the bacterium that is transformed.

2.2. 35 USC section 112, first paragraph

Written description

Claim 1-13 were rejected in the previous action under 35 U.S.C. 112, first paragraph. Rejection of claim 4 is moot because the claim has been canceled.

Rejection of claims 1-3 and 5-13 is maintained. The claims are directed to a large and variable genus of methods of using of integrants of *Bacillus licheniformis* and *Bacillus subtilis* species having at least one heterologous *kerA* gene inserted into their chromosome. The claims are directed to the use of a large genus of transformants comprising one or several copies of any heterologous *kerA* gene. Applicants teach B. licheniformis having its own kerA gene integrated in at least one copy. However, the kerA gene from B. licheniformis is not a heterologous gene for B. licheniformis.

Applicants' attention is turned to the fact that integrants of *B. licheniformis* they describe contain the homologous *kerA* gene in their chromosome.

Regarding B. subtilis, the specification teaches the expression of keratinase of B. licheniformis in B. subtilis on page 6, Table 2. On page 9, the last paragraph, however, Applicants teach that transfomants of B. subtilis were not integrants. Thus, the disclosure fails to teach the invention as claimed, i.e., B. licheniformis or B. subtilis having at least one heterologous kerA gene integrated into its genome. Furthermore, in preparation of their transformants/integrants Applicants used only one kerA gene, which is B. licheniformis kerA. The claims, however, are directed to the integrants having integrated any kerA gene which is heterologous for B. licheniformis or B. subtilis, i.e., to a large genus of integrants comprising a large genus of kerA genes. The only species of kerA genus, i.e., kerA gene of B. licheniformis does not provide an identifying characteristcs of all kerA genes from any organism or man-made. Such genes are encompassed by broad scope of the claims. For the presented reasons, one of skills in the art is not convinced that Applicants were in possession of the claimed invention at the time the application was filled.

In addition, claim 6 is rejected because the Applicants fail to teach *kerA* gene of *Bacillus subtillis*. This is a complete lack of written description. For that reasons, one of skills in the art is not convinced that Applicants were in possession of the claimed invention at the time the application was filled.

Furthermore claim 12 is directed to a large genus of constitutive promoter to be associated with the coding sequences of KerA gene. The genus of constitutive

promoters is not sufficiently described in the disclosure, because providing the P43 promoter does not provide the structural characteristics of the whole genus of the constitutive promoters. Thus, one of skills in the art is not convinced that Applicants were in possession of the claimed invention at the time the application was filled.

Enablement

Claim 1-13 were rejected in the previous Office Action. Rejection of claim 4 is moot, because the claim have been canceled.

Rejection of claims 1-3, and 5-13 is maintained, because the specification, while being enabling for a method of use of a recombinant *Bacillus subtilis* having at least one heterologous *kerA* gene of *Bacillus licheniformis* inserted into *B. subtilis'* chromosome, does not reasonably provide enablement for B. subtilis or B. licheniformis integrant having any heterologous *kerA* gene inserted into its chromosome.

As explained in the previous action, while enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed as to make and use the claimed invention. Specifically, the specification does not instruct as to the structure or origin of any (i.e., all) *kerA* genes to be used. Providing one *kerA* gene of *B. licheniformis* does not provide a guidance as to the structure of all *kerA* gene that are to be used to make the invention. One skilled ion the art realizes that expression of any kerA gene in B. subtilis and B. licheniformis is not necessary obvious taking into account differences in

code usage, ribosome binding site as well as difference in signal sequences between the cell of origin of the gene and B. subtilis and B. licheniformis. In conclusion, without a guidance regarding the structure/origin of *kerA* gene, the experimentation left to skilled artisan is improperly extensive and undue.

Response to Applicant' arguments

Applicants' response to rejection of claims 1-3, and 5-13 under 35 USC 112 first paragraph, appears to argue that the amendment to claim 1 to limit the claim to B. subtilis or B. licheniformis having a ker A gene integrated overcomes the rejections of not only claim 1 but also claim 2-3 and 5-13. The reasons for not withdrawing the rejection made in the previous action are presented above in paragraph **2.2.,** sections Written description and Enablement.

Furthermore, Applicants position regarding rejection of Claim 6 as lacking written description of kerA gene of Baccillus subtilis is that the specification on page 3, third paragraph, contains the sentence "kerA gene has been cloned and expressed from B. subtilis" provides for kerA gene of that species.

Applicants' argument is found not persuasive, because the quoted passage of page 3 relates no doubts to expression of the kerA gene of B. licheniformis in B. subtilis.

2.2. 35 U.S.C. 103

Claims 1, 4, 6, 7 and 9-13 were rejected under 35 U.S.C. 103(a) in the previous action as obvious over Lin et al., (Nucleotide Sequence and Expression of *kerA*, the

Gene Encoding a Keratinolytic Protease of *Bacillus licheniforms* PWD-1, Applied and Environmental Microbiology, 1995, 61, 1469-1474, included in the IDS) in view of van der Laan et al. (Cloning, Characterization, and Multiple Chromosomal Integration of a *Bacillus* Alkaline Protease Gene, Applied and Environmental Microbiology, 1991, 57, 901-909, included in the IDS) and the product of the Dutch Firm DSM, which is integrative plasmid pLAT8 specific for *Bacillus*.

Rejection of claim 4 is moot because the claim has been cancelled. Rejection of claims 1, 6, 7 and 9-13 is maintained.

Response to Applicants arguments

Applicants argue that in order to establish a prima facie case of obviousness three criteria must be met:

1) the sited reference or combination of references must teach or suggest all the claim recitation recitations

2) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings in order to arrive at the claimed invention.

3) there must be a reasonable expectation of success.

Applicants' position is that not all the recitations of the rejected claims are found in the combination of cited references, because

a) Laan et al teach chromosomal integration of Bacillus alkaline protease gene and not a keratinase gene, and

b) the combination of the cited references also fails to teach that the recombinant Bacillus produces greater quantities of keratinase than wild type.

Regarding a), the reference(s) used in 103 rejection does not need to teach all the claims recitation exactly as in claims, otherwise it would be a 102 rejection and not an obviousness rejection. The language "suggest all" stands for that fact. Secondly, Lann et al teaches integration of a serine protease gene from one Bacillus species into the chromosome of another Bacillus species. In the instant application keratinase is a serine protease and the disclosed kerA gene from one bacillus species (B. licheniformis) is integrated into another bacillus species, i.e. B. subtilis.

Regarding b) the enzyme expressed from the heterologous gene in a host cell is by definition not expressed in the wild type of the host cell, because the wild type host does not have this gene. Furthermore, Laan et al teach that serine protease they expressed from the heterologous gene integrated into B. subtillis was produced in greater amount in the bacterium having the gene integrated as compared with that comprising plasmid only; see the abstract, Table 1 and comments on protease production, page 905, right column, third paragraph.

As to Applicants point 2) and 3) those skilled in the art are aware of usefulness of keratinase for tens of years as evidenced by numerous publications quoted by Applicants in IDS. The state of art also suggests to integrate the genes to host

chromosome to get stable transformants, as Laan et al did in 1991. Laan, as explained in the previous action, provided the expectation of success, because he proved that serine protease gene from one bacillus spiecies can be successfully integrated in into the chromosome of another bacillus species and the enzyme be produced more efficiently than when the host contains the same plasmid without the gene.

In conclusion the obviousness rejection of claims 1, 6, 7 and 9-13 is sustained.

3. Conclusion

All claims are rejected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka whose telephone number is (571) 272-0944. The examiner can normally be reached on Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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